ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.04.052

N-Acetylcysteine Versus Fenoldopam Mesylate to Prevent Contrast Agent-Associated Nephrotoxicity

Carlo Briguori, MD, PhD,*† Antonio Colombo, MD,† Flavio Airoldi, MD,† Anna Violante, MD,* Alfredo Castelli, MD,† Pasquale Balestrieri, MD,* Pietro Paolo Elia, MD,* Bruno Golia, MD,* Stefano Lepore, MD,* Guido Riviezzo, MD,* Pierfranco Scarpato, MD,* Mariateresa Librera, MD,* Amelia Focaccio, MD,* Bruno Ricciardelli, MD*

Naples and Milan, Italy

OBJECTIVES We performed a study to assess the efficacy of fenoldopam mesylate (a specific agonist of the dopamine-1 receptor) as compared with N-acetylcysteine (NAC) in preventing contrast agent-associated nephrotoxicity (CAN).

BACKGROUND Prophylactic administration of NAC, along with hydration, prevents CAN in patients with chronic renal insufficiency who are undergoing contrast media administration. Preliminary data support the hypothesis that fenoldopam might be as effective as NAC.

METHODS One hundred ninety-two consecutive patients with chronic renal insufficiency, referred to our institution for coronary and/or peripheral procedures, were assigned randomly to receive 0.45% saline intravenously and NAC (1,200 mg orally twice daily; NAC group; n = 97) or fenoldopam (0.10 μg/kg/min; fenoldopam group; n = 95) before and after a nonionic, iso-osmolality contrast dye administration.

RESULTS Baseline creatinine levels were similar in the two groups: NAC group = 1.72 mg/dl (interquartile range, 1.55 to 1.90 mg/dl) and fenoldopam group = 1.75 mg/dl (interquartile range, 1.62 to 2.01 mg/dl) (p = 0.17). An increase of at least 0.5 mg/dl of the creatinine concentration 48 h after the procedure occurred in 4 of 97 patients (4.1%) in the NAC group and in 13 of 95 patients (13.7%) in the fenoldopam group (p = 0.019; odds ratio 0.27; 95% confidence interval 0.08 to 0.85). The amount of contrast media administration was similar in the two groups (NAC group = 160 ± 82 ml; fenoldopam group = 168 ± 104 ml; p = 0.54).

CONCLUSIONS N-acetylcysteine seems to be more effective than fenoldopam in preventing CAN. (J Am Coll Cardiol 2004;44:762–5) © 2004 by the American College of Cardiology Foundation

Radiocontrast media can lead to a reversible form of acute renal failure that, especially in high-risk patients, may require transient dialysis and may impair in-hospital and long-term outcomes (1–3). The two major mechanisms of contrast-associated nephrotoxicity (CAN) are renal vasoconstriction (4) and direct toxic effects of the contrast agents (5,6). Recommendations to prevent CAN are: 1) periprocedural hydration (7), 2) the use of a low- or iso-osmolality contrast (8–11), and 3) limiting the amount of contrast agent (12). Recently, two additional strategies associated with to hydration aroused considerable interest: N-acetylcysteine (NAC) and fenoldopam mesylate; the former, a potent antioxidant compound, may prevent the direct oxidative tissue damage by scavenging reactive oxygen species (13), whereas the latter, a specific dopamine-1 receptor agonist that causes peripheral vasodilatation via stimulation of postsynaptic dopamine-1 receptors (14), may prevent renal vasoconstriction (15–18).

We performed a prospective, randomized trial comparing the safety and prophylactic effectiveness of NAC plus hydration versus fenoldopam mesylate plus hydration in patients with chronic renal insufficiency undergoing coronary or peripheral artery procedures.

From the *Laboratory of Interventional Cardiology and Department of Cardiology, Clinica Mediterranea, Naples, Italy; and †Laboratory of Interventional Cardiology, "Vita e Salute" University School of Medicine, Milan, Italy.

Manuscript received March 11, 2004; revised manuscript received April 14, 2004, accepted April 19, 2004.

METHODS

Patient population. This is a prospective, randomized study conducted in our institutions from March to December 2003. The local ethics committee ("Vita e Salute" University School of Medicine, Milan, Italy) approved the study protocol. All patients gave written informed consent. Consecutive patients scheduled for elective coronary and/or peripheral angiography and/or angioplasty were eligible for the study if they had chronic impairment of renal function (serum creatinine concentration ≥1.5 mg/dl and/or creatinine clearance <60 ml/min) and stable serum creatinine concentrations. Patients were randomly assigned to receive intravenous saline plus NAC (NAC group) or fenoldopam mesylate (fenoldopam group) before and after administration of iodixanol (Visipaque, 320 mg iodine/ml, Amersham Health, Amersham, United Kingdom) a non-ionic, iso-osmolality contrast agent. Saline (0.45%) was given intravenously at a rate of 1 ml/kg of body weight/h (0.5 ml/kg for patients with left ventricular ejection fraction [LVEF] <40%) for 12 h before and 12 h after administration of the contrast agent (7). N-acetylcysteine (Fluimucil, Zambon Group Spa, Milan, Italy) was given orally at a dose of 1,200 mg twice daily in the NAC group on the day before and on the day of administration of the contrast agent for a total of two days (19). Fenoldopam mesylate (Corlopam, Elan Pharma Italia, Rome, Italy) infusion was started at least 1 h before the procedure at 0.10 μg/kg/min, maintained

Abbreviations and Acronyms
CAN = contrast agent-associated nephrotoxicity
LVEF = left ventricular ejection fraction
NAC = N-acetylcysteine

during the procedure, and continued for 12 h after the procedure. The dosage was downtitrated or discontinued in cases of hypotension or tachycardia (20). Severe hypotension was defined as a systolic blood pressure <90 mm Hg. None of the patients received theophylline, dopamine, mannitol, or furosemide during the study. Serum creatinine, blood urea nitrogen, sodium, and potassium were measured immediately before and 48 h after administration of the contrast agent; additional measurements were performed in all cases of significant impairment of renal function. Creatinine clearance was calculated by applying the Cockcroft-Gault formula (21).

Study end point. Contrast agent-associated nephrotoxicity was defined as an increase in the serum creatinine concentration ≥0.5 mg/dl of the baseline value 48 h or need for dialysis after administration of the contrast media (8). Acute renal failure requiring dialysis was defined as a decrease in renal function necessitating acute hemodialysis, ultrafiltration, or peritoneal dialysis in the first five days postintervention.

Statistical analysis. A total sample size of 180 subjects randomized with a 1:1 allocation ratio was calculated to achieve a power $(1 - \beta)$ of 90% to detect a difference of 10% between the null hypothesis that both group proportions are 5% and the alternative hypothesis that the proportion in the NAC group is 5% (19) and in the fenoldopam group is 15% (17,20) using a two-sided chi-square test with a significance level of 0.05. Continuous variables are given as mean ± 1 SD or median and interquartile ranges. An unpaired Student *t* test was performed to determine differences between mean values for continuous variables when appropriate. Categorical variables were analyzed by using the chi-square test. Creatinine concentration was not normally distributed; therefore, the nonparametric Wilcoxon rank-sum test and Mann-Whitney *U* test were used to assess differences. Probability values <0.05 were considered significant. Data were analyzed with SPSS 10.0 (SPSS Inc., Chicago, Illinois) for Windows.

RESULTS

Clinical characteristics. The clinical and biochemical characteristics of the 192 enrolled patients are shown in Tables 1 and 2. Three patients experienced side effects in the fenoldopam group that necessitated premature drug infusion discontinuation: two patients had severe hypoten-

Table 1. Clinical Characteristics of Patients Treated With N-Acetylcysteine and With Fenoldopam

	NAC Group (n = 97)	Fenoldopam Group (n = 95)	p Value
Age (yrs)	68 ± 9	69 ± 8	0.30
Male	84 (87%)	79 (83%)	0.51
Weight (kg)	75 ± 15	74 ± 12	0.80
Height (m)	1.68 ± 0.7	1.68 ± 0.6	0.98
Body mass index (kg/m^2)	26 ± 5	26 ± 3	0.94
Blood pressure (mm Hg)			
Systolic	136 ± 19	137 ± 20	0.80
Diastolic	77 ± 10	75 ± 11	0.22
Mean	97 ± 12	96 ± 12	0.55
Left ventricular ejection fraction (%)	52 ± 12	51 ± 11	0.61
Systemic hypertension	74 (77%)	72 (76%)	0.94
Diabetes mellitus	49 (50.5%)	49 (52.1%)	0.83
Peripheral chronic artery disease	31 (32%)	36 (38%)	0.33
Drugs			
ACE inhibitor	52 (54%)	61 (65%)	0.12
Calcium channel blocker	36 (37%)	47 (50%)	0.14
Angiotensin II receptor inhibitor	15 (16%)	12 (13%)	0.51
Diuretic	44 (46%)	36 (38%)	0.27
Beta-blockers	38 (39%)	42 (44%)	0.49
Performed procedure			
Coronary angiography	43 (44%)	45 (47%)	0.67
PCI	20 (21%)	13 (13.5%)	0.10
Coronary angiography and ad hoc PCI	24 (25%)	24 (25%)	0.93
Peripheral angiography	4 (4%)	9 (9.5%)	0.14
Peripheral angioplasty	6 (6%)	4 (3.5%)	0.54
Total amount of hydration (ml)	1,798 ± 348	1,805 ± 283	0.99
Volume of contrast media (ml)	160 ± 82	168 ± 104	0.54
>140 ml	54 (55%)	48 (50.5%)	0.52

ACE = angiotensin-converting enzyme; NAC = N-acetylcysteine; PCI = percutaneous coronary intervention.

Table 2. Biochemical Characteristics of Patients Treated With N-Acetylcysteine and With Fenoldopam

	NAC Group (n = 97)	Fenoldopam Group (n = 95)	p Value
Serum creatinine, median (IQR), mg/dl			
Baseline	1.72 (1.55–1.90)	1.75 (1.62–2.01)	0.17
After 48 h	1.60 (1.40–1.86)	1.71 (1.48–2.03)	0.77
Serum creatinine (>2.5 mg/dl)	9 (9%)	11 (11.5%)	0.45
Creatinine clearance (ml/min)	43 ± 16	40 ± 14	0.33
Serum urea nitrogen (mg/dl)			
Baseline	66 ± 20	70 ± 21	0.27
After 48 h	60 ± 26	63 ± 21	0.32
Serum sodium (mEq/l)			
Baseline	141 ± 3	141 ± 3	0.30
After 48 h	140 ± 8	141 ± 4	0.44
Serum potassium (mEq/l)			
Baseline	4.9 ± 0.6	4.5 ± 0.6	0.76
After 48 h	4.9 ± 0.6	4.5 ± 0.6	0.75

IQR = interquartile range; NAC = N-acetylcysteine.

sion (one patient 2 h and the other 4 h after the procedure), and one patient had an allergic reaction (skin rash and vomiting) before the procedure. We found a trend to an higher absolute decrease in systolic blood pressure in the fenoldopam group than in the NAC group (−17 ± 20 mm Hg vs. −11 ± 25 mm Hg; p = 0.068). In contrast, the decrease in diastolic (−9 ± 11 mm Hg vs. −9 ± 14 mm Hg; p = 1.00) and mean (−11 ± 12 mm Hg vs. −8 ± 15 mm Hg; p = 0.30) blood pressure was similar in the two groups.

Contrast agent-associated nephrotoxicity. Contrast agent-associated nephrotoxicity occurred in 4 of 97 patients in the NAC group (4.1%) and in 13 of 95 patients in the fenoldopam group (13.7%; p = 0.019; odds ratio 0.27; 95% confidence interval 0.08 to 0.85) (Fig. 1). Contrast agent-associated nephrotoxicity occurred in 5 of 11 (45.5%) patients with serum creatinine level >2.5 mg/dl in the fenoldopam group versus 1 of 9 (11%) patients in the NAC group (p = 0.095). In the 98 diabetic patients, renal function deterioration occurred in 4 of 49 (8.2%) patients in the fenoldopam group and in 3 of 49 (6.1%) in the NAC group (p = 0.72). In the 23 patients with LVEF <40%, renal function deterioration occurred in 4 of 13 (13.3%) in fenoldopam group and none of the 10 patients in the NAC group (p = 0.23). In patients with LVEF ≥40%, renal function deterioration occurred in 9 of 72 (12.5%) patients in fenoldopam group and 4 of 87 (4.5%) in the NAC group (p = 0.085). No cases of CAN were observed in the 16 diabetic patients with LVEF <40% (7 patients in the fenoldopam group and 9 in the NAC group). In the fenoldopam group, mean blood pressure lowering was similar in patients with and without CAN (−11 ± 11 mm Hg vs. −11 ± 10 mm Hg; p = 0.95) and in patients with LVEF <40% and ≥40% (−13 ± 9 mm Hg vs. −10 ± 12 mm Hg; p = 0.39).

Renal failure requiring dialysis occurred in one patient enrolled in the fenoldopam group (1.1%): this patient subsequently experienced in-hospital death. Length of in-hospital stay (from admission to discharge) was longer in the fenoldopam group than NAC group (5.0 ± 10 days vs. 2.9 ± 2.7 days; p = 0.049).

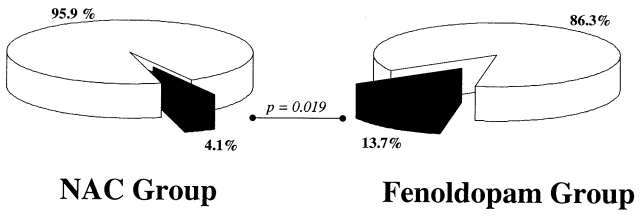

Figure 1. Schematic representation of the distribution of the occurrence of contrast agent-associated nephrotoxicity in patients treated with the N-acetylcysteine (NAC group) and with fenoldopam mesylate (fenoldopam group). **Filled areas** = cases with event; **open areas** = cases without event.

DISCUSSION

Contrast agent-associated nephrotoxicity represents the third cause of in-hospital renal function deterioration after decreased renal perfusion and postoperative renal insufficiency (22). An optimal strategy to prevent CAN remains unknown. Recently, two additional strategies associated with hydration aroused considerable interest: NAC and fenoldopam mesylate.

NAC and CAN. The quite low incidence of CAN in the NAC group (4.1%) observed in the present study confirms what we previously reported (19). A potent antioxidant that scavenges a wide variety of oxygen-derived free-radicals, NAC may prevent CAN by avoiding direct oxidative tissue damage and also by improving renal hemodynamics (23–25). Tepel et al. (13) first reported that NAC plus hydration is more effective than hydration alone in preventing CAN. A recent meta-analysis evaluating more than 800 high-risk patients enrolled in randomized controlled trials supports that NAC plus hydration significantly reduces the risk of CAN in patients with chronic renal insufficiency (26). We used a dosing regimen that was double (1,200 mg orally

twice daily) (19) that suggested by Tepel et al. (13) because the antioxidant effect of NAC seems to be dose-dependent (27). With large volumes of contrast dye, the beneficial effect of the NAC may be evident only by using a dosing regimen double that suggested by Tepel et al. (13).

Fenoldopam and CAN. Fenoldopam mesylate is the first selective dopamine-1 receptor agonist approved for the in-hospital treatment of patients with severe hypertension (14). A low dosage of fenoldopam that does not decrease systemic blood pressure produces dopamine-1 receptor-mediated dose-related renal vasodilatation, diuresis, and natriuresis (14). In dogs, fenoldopam protects against the acute renal vasoconstriction that may be induced by contrast agents (16). The protective effect of fenoldopam in patients at risk of CAN might involve its ability to selectively increase blood flow to the renal medulla. Although preliminary studies suggest that the administration of fenoldopam protects against CAN (16–18), our finding confirms the results of the recent Controlled Multicenter Trial Evaluating Fenoldopam Mesylate for the Prevention of Contrast-Induced Nephropathy (CONTRAST) trial (20), which suggested that fenoldopam mesylate is ineffective in preventing further renal function deterioration in patients with chronic renal insufficiency receiving iodinated contrast. According to these findings and considering also the high cost of this drug, a strategy of hydration plus fenoldopam mesylate should not be used as a prophylactic measure to prevent CAN.

Study limitations. Our study was not blinded. Fenoldopam mesylate increases renal blood flow in a dose-dependent manner (14); hence, a dose >0.10 μg/kg/min may be needed to achieve an optimal prophylactic action against CAN. Increasing the dose, however, increases the risk of hypotension with resultant intrarenal vasoconstriction.

Reprint requests and correspondence: Dr. Carlo Briguori, Interventional Cardiology, Clinica Mediterranea, Via Orazio, 2, I-80121, Naples, Italy. E-mail: briguori.carlo@hsr.it.

REFERENCES

1. Parfrey PS, Griffiths SM, Barrett, BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med 1989;320:143–9.
2. Chertow GM, Christiansen CL, Cleary DP. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. Arch Intern Med 1995;155:1505–11.
3. McCullough PA, Wolyn R, Rocher LL, Levine RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997;103:368–75.
4. Weisberg LS, Kurnik PB, Kurnik, BR. Radiocontrast-induced nephropathy in humans. Role of renal vasoconstriction. Kidney Int 1992;41:1408–15.
5. Bakris GL, Lass N, Gaber AO, Jones JD, Burnett Jr. JC Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. Am J Physiol 1990;258:F115–20.
6. Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. Am J Kidney Dis 1997;29:465–77.
7. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416–20.
8. Schwab SJ, Hlatky MA, Pieper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. N Engl J Med 1989;320:149–53.
9. Barrett BJ, Carlisle EJ. Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 1993; 188:171–8.
10. Steinberg EP, Moore RD, Powe NR, et al. Safety and cost effectiveness of high-osmolality as compared with low-osmolality contrast material in patients undergoing cardiac angiography. N Engl J Med 1992;326:425–30.
11. Aspelin P, Aubry P, Frausson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angioplasty. N Engl J Med 2003;348:491–9.
12. Cigarroa, RG, Lange, RA, Williams, RH, Hillis, LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 1989;86:649–52.
13. Tepel M, Van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343: 180–4.
14. Murphy MB, Murray C, Shorten GD. Fenoldopam—a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. N Engl J Med 2001;345:1548–57.
15. Bakris GL, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role of dopamine receptors. Kidney Int 1999;56:206–10.
16. Madyoon H, Croushore L, Weaver D, Mathur V. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. Cathet Cardiovasc Intervent 2001;53:341–5.
17. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am Heart J 2002;143:894–903.
18. Kini AS, Mitre CA, Kim M, Kamran M, Reich D, Sharma SK. A protocol for prevention of radiographic contrast nephropathy during percutaneous coronary intervention: effect of selective dopamine receptor agonist fenoldopam. Cathet Cardiovasc Intervent 2002;55: 169–73.
19. Briguori C, Colombo A, Violante A, et al. Standard versus double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. Eur Heart J 2004;25:206–11.
20. Stone GW, McCullough PA, Tumlin JA, et al. Fenoldopam mesylate for the prevention of contrast-induced nephrotoxicity. JAMA 2003; 290:2284–91.
21. Cockcroft DW, Gault MH. Prediction of creatine clearance from serum creatine. Nephron 1976;16:31–41.
22. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital acquired renal insufficiency: a prospective study. Am J Med 1983;74: 243–8.
23. Tariq M, Morais C, Sobki A, Al Sulaiman M, Al Khader A. N-acetylcysteine attenuates cyclosporin-induced nephrotoxicity in rats. Nephrol Dial Transplant 1999;14:923–9.
24. DiMari J, Megyesi J, Udvarhelyi N, Price P, Davis R, Safirstein R. N-acetylcysteine ameliorates ischemic renal failure. Am J Physiol 1997;272:F292–8.
25. Andrews NP, Prasad A, Quyymi AA. N-acetylcysteine improves coronary and peripheral vascular function. J Am Coll Cardiol 2001; 37:117–23.
26. Birck R, Krzossok S, Markowetz F, Schnulle P, van der Woude F, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet 2003;362:598–603.
27. Cotgrease I, Moldeus P, Schuppe I. The metabolism of N-acetylcysteine by human endothelial cells. Biochem Pharmacol 1991;42:13–6.